

ON THREE CASES OF PIGMENTATION OF THE LARGE
INTESTINE.

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CASE I.

Margaret M., aged 73 years was admitted on June the 14th 1912 to Ward 8.R.I.E. under Professor Caird's charge, suffering from jaundice.

The history was that she had been jaundiced for three months. It had begun gradually and become progressively deeper. Her mind was feeble and a full history could not be obtained.

Her previous health had apparently been good. She



had had some rheumatism. There was no history of syphilis nor of any course of mercury. There was no history obtained as to the regularity of the bowels.

On admission she was weak and very ill. Her bowels moved daily with aperients. She had two five grain doses of calomel while in Hospital. The stools were clay coloured and urine bile stained. Her skin was deeply jaundiced. She became progressively weaker and died on June 22nd, eight days after admission.

Clinical diagnosis "Obstructive^{ive} Jaundice".

Post mortem. June 24th, thirty-six hours after death, performed by Dr. Shennan in the Pathological Department R.I.E.

Extracts from Post mortem Report:-

Body emaciated some oedema of lower limbs, very marked jaundice,

Some old stringy adhesions left pleura, similar ones right side.

Lungs:- Congestion and slight oedema; one or two patches of pneumonic consolidation at bases.

Gall bladder much dilated.

Common duct greatly distended.

Pancreas:- Numerous small areas of fat necrosis.

Liver:- Numerous small abscesses projecting on the surface - probably suppurative cholangitis.

Spleen-acute softening and post mortem change. Small infarct in one portion.

Kidneys:- biled stained, show cloudy swelling, cap-

sules adherent. Surface after stripping is slightly granular.

Heart:- Some hypertrophy of the left ventricle, and Some thickening of mitral valve.

Intestines:-

Appendix dilated at the tip, and surrounded by old adhesions.

Small Intestine:- healthy in appearance.

Large Intestine:- full of clay coloured faeces.

Well marked melanosis.

Post mortem diagnosis:-

Obstructed^{ive} Jaundice, obstructed^{ive} cholangitis.

Chronic Myocarditis.

Slight chronic interstitial nephritis.

Lobular pneumonia.

Melanosis of large intestine.

The suprarenals were healthy. There was no sign of enlargement or pigmentation of the lymph glands either in relation to the intestine or in other parts of the body.

The specimen, hardened in formalin, treated with spirit, and preserved in Glycerine and water was examined seven months after the post mortem. It consists of the last foot of the small intestine, and the large intestine as far as the sigmoid flexure. Externally it is normal in appearance, except that there are traces of old inflammatory adhesions in the neighbourhood of the appendix; and that this latter is slightly bulbous at its distal extremity.

Internally the mucous membrane of the portion of the ileum preserved is healthy in appearance. It shows no bile staining and no pigmentation; it is smooth and greyish white in colour. The mucous membrane of the large intestine shows throughout its length a dark brown pigmentation. This pigmentation begins exactly at the ileo-caecal valve. The ileal side of the valve is quite free from pigment - the caecal side is darkly pigmented. The line between the pigmented and the normal mucous membrane is sharp and straight, corresponding to the margin of the valve.

The intensity of the pigmentation varies. In the caecum it is on the whole dark, gold and brown in colour, but not quite uniform; there are irregular areas of perhaps several inches in their longest diameter which are lighter coloured, and rather yellowish golden than brown. Other parts are much darker and have a sooty appearance. There is no sharp margin between these areas of different intensity, but the colour gradually changes from one to the other.

Lower down in the bowel the general colour is rather darker, the lighter coloured portions are not so evident, and the dark, almost soot-like appearance predominates.

In the region of the ^{ig}semoid flexure the bowel is very darkly pigmented, and the lighter golden yellow areas do not occur.

The mucous membrane of the appendix is darkly

pigmented in its proximal third; beyond this there is a slight constriction, and the distal portion is filled with mucus. The mucous membrane of this portion shows no ⁴⁹pigmentation.

Closer examination shows that the pigmentation presents a kind of mosaic appearance. Over the whole surface of the mucous membrane there is a fine network of intersecting lines enclosing little areas of pigmented bowel. These lines are light yellowish in colour, about $\frac{1}{4}$ mm. in diameter and inclose polyhedral areas of pigmented bowel of a diameter varying from about 1 mm. to 2 or 3 mm.

The network is most distinct in the lighter coloured areas, ^{but} that is to be seen all over the surface of the bowel.

Along the taenia coli in some parts the areas enclosed are more rectangular in shape. There is a tendency for the lines to run parallel to the direction of the taenia, and the cross lines to be at right angle to these, so that the enclosed areas are parallel again.ograms.

Apart from the pigmentation the mucous membrane appears quite healthy. There is no evidence of ulceration, inflammation, or scars. The bowel wall appears normal.

There is no evidence of any pigment in the lymphatics.

The recorded cases of total pigmentation of the large intestine are few in number. It is a condition which is associated with no apparent clinical symptoms. The patients in whom it has been found postmortem, have been the subject of varying diseases, have before death presented few, if any symptoms, by which such a condition could be diagnosed, and the condition has been found as it were accidentally, in the course of a routine post mortem examination. In view of this fact there is some probability that the condition is not as rare as has been supposed. Professor Pick of Berlin, who has collected the reported cases, and published six cases of his own (Berliner Klinische Wochenschrift 1911 SS. 840 and 884), found three cases in about six thousand post mortem examinations in the Friedrichshain Hospital in Berlin and a thousand other post mortems from outside districts, and he quotes the fact that Solger, working in the Grawitz Institute saw five cases (referring only to one type of pigmentation, i.e. melanosis) in four months. It is very probable then, as the condition produces no visible change on the outer surface of the gut by which its presence may be recognised, that many cases have been overlooked, and were the large bowel to be examined thoroughly in all post mortem examinations, not only might the condition be found to be one of no extreme rarity, but earlier stages in its production might possibly be brought to light, and a better opportunity be afforded for a study of its clinical

significance and the causes underlying its production.

Pigmentation in this site is in the main one of four chief types.

The first type is that due to post mortem change in the bowel - the so-called "pseudo-melanosis". The bowel, and especially the lower bowel, owing to the number of bacteria which it normally contains, is of course one of the first tissues in the body to undergo post mortem change. This condition has however characteristic appearances, which cannot be confused with the other forms. The dirty dark green appearance presented by a bowel which has undergone this change does not resemble the yellow staining of bile pigment, nor the golden brown of melanosia, and mercuric infiltration, nor the dark sooty black of lead and bismuth; the tissue in these cases also always gives, more or less marked, the Prussian blue re-action.

The second type of pigmentation is that due to staining by bile pigment. The appearance of this also is characteristic. The history of the first case under discussion - the fact that she had been suffering for some while from obstructive jaundice, made the exclusion of bile staining especially important. The specimen, however, was in no way suggestive of such a condition. The dark golden brown colouration, with the mosaic pattern, the freedom of the small intestine, and in microscopical sections,

of the superficial epithelium were all exclusive of it.

In the chemical tests for bile and bile acids negative results were in all cases obtained.

The third type of pigmentation is that due to a deposition of metals, especially mercury, lead, bismuth, less frequently silver, perhaps arsenic, antimony and some others.

The appearance produced by the first two of these may bear a remarkable resemblance both macroscopically and microscopically to that of the fourth type, that is of melanosis.

The first recorded case of pigmentation due to mercury was that of C. J. Williams, whose case is given below among those collected by Pick (Loc. Cit.). In describing the specimen Williams says:- "The internal surface of the large intestine was remarkably black, mottled in parts with patches of a lighter hue, the colour commencing at the ileo-caecal valve, and contrasting strongly with the light colour of the small intestine. The mucous membrane was smooth and shiny, and there was no ulceration nor abrasion of the surface, but the whole presented the appearance of a toad's back".

"On microscopic examination of sections of the intestine, the colouring matter was found to be deposited in the sub-mucous tissues between the

epithelial and muscular coat, and to consist of:-

- (1) Large black opaque masses of irregular form,
- (2) Minute granules, sometimes separate, and sometimes grouped together".

Portions of the ~~Sa~~ecum were then tested for mercury by careful drying, boiling with hydrochloric acid, addition of potassium chlorate, and the resulting green solution boiled with copper scrapings. These were placed in a small tube with a bulb at one end, which was heated. Well marked globules of mercury were deposited in the cool portion of the tube.

The description of the specimen - the limitation of the pigmentation to the large intestine, with the sharp margin at the ileo-caecal valve, macroscopic appearance - that of a "toad's back", with the areas of ~~the~~ lighter pigmentation, and microscopically, the limitation of the deposit to the area between the epithelium and muscular coats (though Williams describes it as "sub-mucous") all tally very closely with the cases described by Pick as true melanosis.

~~Th~~Acform of the pigment - in larger masses, and finer granules, apparently always amorphous, corresponds closely to Pick's description.

Williams makes no mention as to whether the pigment was intra - or extra - cellular, nor as to whether the lymphatics were involved or not.

Williams' case had an undoubted and remarkable history of the taking of mercury over a long period,

and there seems to be no doubt that the pigmentation was in fact due to this metal.

H. D. Rolleston, also cited amongst Pick's cases, showed a specimen. He says, "The caecum and colon are shown, they are uniformly pigmented. There was no pigmentation of the small intestine. There was no evidence of ulceration or inflammation in any part of the alimentary canal".

Examined chemically by Dr. Rideal it was reported that the tissue contained a mercury compound soluble in hydrochloric acid.

"Microscopically - amorphous masses are seen to be situated in the mucous membrane apparently in and between the cells of Lieberkühn's crypts; there are no pigmented granules below the muscularis mucosae.

Since the colon contains mercury, and the mucous membrane amorphous pigment, I have thought it probable that the pigmentation is due to the deposit of mercury in the mucous coat of the bowel."

With regard to lead, Newton Pitt's case shows that here also the resemblance may be a close one. His case - cited later amongst those of Pick's, was an undoubted example of lead deposit. There was abundant clinical support besides the chemically determined presence of large quantity of lead in the intestinal tissue. He says, "At the inspection the whole of the small intestine was healthy, but the

caecum and colon down to the anus were deeply pigmented. In the region of the caecum it was almost black".

In the coloured plate which accompanies his account of the case (and which depicts a specimen after it had lost a good deal of its colouration owing to its preservation in spirit), the small intestine is shown as quite free from pigment. The large intestine shows mottled pigmentation varying in colour from very dark brown to lighter more golden colour. The network or mosaic appearance described by Pick in his cases, is distinctly portrayed.

As regards bismuth Rossle, describing three fatal cases of poisoning by Dermatol (bismuth subgallate) (Munsch. Med. Wochenschr. 1911 No. 5.S. 279) says, "The section shows a brown-black pigmentation of the colon, like one sees oftenest in cases of the at present rare cases of argyria, and in exceptional cases in chronic mercurial poisoning. The dark colour is confined to the large ^{gut} ~~gut~~, stops at the ileo-caecal valve, and is not present in the appendix. The solitary glands stand out as pigment-free spots."

Pick (Loc. Cit.) in discussing these cases of metallic pigmentation, admits their strong resemblance to those cases which he regards as pure melanosis, but thinks that certain well defined differences exist.

1. The absolute limitation of the lesion in the alimentary canal to the large intestine, which is so

characteristic of true melanosis, does not, he says, hold good as a rule for mercury and bismuth.

2. The absence in true melanosis of the slightest sign of inflammation, remains of inflammatory processes, or scars in the mucous membrane, the absence of such symptoms as tremor, salivation, etc. as would occur with chronic mercurial poisoning, or of haemosiderosis as would occur with bismuth, as a result of the destruction of red blood corpuscles, not only in the spleen, liver etc., but also in the mucous membrane of the gut.

3. The pigmentation in the cases of metal poisoning must be produced by the metals themselves in one of two ways; (a) mercury sulphide or bismuth sulphide is formed by the action of the sulphuretted hydrogen in the gut, acting on the metallic salts circulating in the capillaries, and the sulphide thus formed is deposited in the tissues as insoluble material, or (b) polymorphonuclear leucocytes take up the metal itself from the blood, and transfer it to the superficial layer of the gut wall. In these cells the pigment then becomes dark without the action of sulphuretted hydrogen.

Therefore the presence of the metal in question could be definitely proved by chemical re-action, and in none of his cases, though all were tested carefully for metals, was any trace of them found.

The fourth type of pigmentation met with in the bowel is that known as melanosis. Except those published by Pick there have been no cases recorded.

The very close resemblance of the first of the writer's cases to these cases of Pick's, led at the time of the post mortem to the diagnosis of melanosis, and the chemical re-action of the material to hand was found to correspond closely in many ways to those which are supposed to be characteristic of melanin. In the process of exclusion of the metals, there was found to be, when the tissue was treated in mass, a definite re-action for mercury, and investigations were then undertaken with a view to deciding whether

1. The whole pigmentation was due to a mercurial deposit, or
2. The mercury re-action denoted merely the presence of adventitious mercury, perhaps from the recent administration of mercurial purges, or
3. The pigmentation was due partly to mercury and partly to true melanin.

The clinical data could not provide much help in deciding the question. On the one hand there was no history obtainable of any considerable quantity of mercury having been taken, though on account of the patient's mental state many facts in her past history were incapable of being ascertained, and little importance could be attached to this absence. On the other hand the physiology and pathology of melanin formation is little understood, and any predisposing causes which might have existed in the patient's history and condition must of necessity remain unknown.

The occurrence and mode of formation of melanin.

The deposition of melanin is of wide occurrence both under physiological and pathological conditions; thus it occurs in small quantity in normal human skin - chiefly in the cytoplasm of the cells of the basal layer, and the intercellular spaces between them (Dyson - Pigmentation in Pathological Conditions. Journal of Pathology 1911 page 302), in hair, in pigmented naevi, pigmented tumours such as melanotic sarcomata, in large quantity in negro skin, in the skin following irritation, for instance X rays, etc., in the skin of many animals, and in various structures in some insects.

In relation to the cutis it is of rarer occurrence and has been observed chiefly in relation to larger quantity in the overlying epithelium. Dyson (Loc.Cit.) states that he has never observed any considerable amount of pigment in the cutis without the epithelium being hyper-pigmented.

The origin and mode of formation of the pigment has been much debated, and no settled conclusion is as yet arrived at. There are, or have been, three principle theories:-

1. That it is a product of the blood, being ultimately derived from haemoglobin.

Langhans - from the study of extravasated blood, concluded that it was derived directly from broken down red blood corpuscles.

Demiéville (Virchow's Archives Bd. 81. 1880 S.333) thought that the distribution of pig-

ment in the neighbourhood of small blood vessels suggested its origin from the blood, and thought from the size and shape of the pigment granules that they were simply altered red blood corpuscles.

Scherl (Arch. f. opthalmol. abt. 2. Bd. 39. 1893 S. 130) from his researches with the embryos of certain of the vertebrae supports the view of the formation of the pigment from the blood. He found that the first appearance of pigment in the choroid of the eye corresponded both as regards time and causation with the development of the blood vascular system.

He contends that the pigment is an iron containing derivative of the blood-colouring *matter* which leaves the blood vessels in a soluble form, passes to the tissue fluids, gradually changes its constitution, and becomes altered into spherical drops. He thought that the pigment might be regarded as an excretion, resulting from the destruction of the haemoglobin, and that epithelium played the part of a magazine, where the destruction products were deposited, to be rendered harmless and ultimately got rid of.

This is the oldest of the theories and has been for the most part abandoned. In view of the fact that true melanin gives no re-action for iron, and of its general composition its origin from haemoglobin is thought to be dis-

proved.

2. That it is a product of epithelial cell metabolism.

Mertsching (Virch. Arch. Bd. 116 1889, S 184) from a study of the pigment in the hair concluded that it was derived from the nuclei of epithelial cells undergoing degeneration and that in the skin is formed in the same way.

Jarisch (Arch. f. Dermat u. syph. wien. 1891 Bd. 23 S. 583) from investigation of the skin of frog larvae concluded that it was formed from epidermal cells. He found that the pigmentation of the skin proceeded from without inwards, and that it had no relation to blood colouring matter.

William Dyson (Journal of Pathology 1911, p. 298) on investigating pigment in various sections of epithelium e.g. normal skin, lentigo, pigmented naevi, X ray pigmentation, negro skin, human nipple and areola etc. finds (1) in the epithelium the pigment is accumulated in the basal cells of the epithelium, and in the intracellular lymph spaces. With active pigmentation going on it occurs also in the more superficial layers, becoming less as the surface is approached.

It is arranged ~~that~~ the boundary between the nucleus and the cytoplasm, and distributed from here through the cell. (2) In the cutis the pigment has no regular arrangement. It occurs both in the cells and loose in the

lymphatics, and this loose pigment has often no pigmented cells near it.

The cutis he never found pigmented without hyperpigmentation of the epithelium. He found in some paraffin sections that often some of the pigment had been dissolved, in the case of the epithelium, but not in that of the cutis. He found that this portion was soluble in xylol, chloroform, and alcohol. The basal cells in some cases stained faintly with osmic acid, thus suggesting a fatty nature.

With a view to determining the nature of the pigment he employed Lorraine Smith's method for the staining of fatty substances in tissues. (Lorraine Smith has shown this re-action to be due to the presence of unsaturated lipid molecules).

The method is as follows:- Tissue hardened in formalin cut with a freezing microtome. Sections placed in saturated solution of potassium bichromate and placed (in the solution) in an incubator at 37° centigrade. From day to day a section was taken out and stained for twenty-four hours in Kulschitsky's haemotoxylin solution:- 1% haemotoxylin

2% acetic acid.

The sections were then differentiated for twenty-four hours in a solution of borax

ferrocyanide - Borax 40 grams.
Potassium ferrocyanide 50 grams.
Water 2,000 c.c.

The sections were washed in cold water after each solution. Then dehydrated with alcohol, cleared in xylol and mounted in Canada balsam.

He was able in this way to demonstrate the presence of certain blue staining granules in the cells, and related their presence to the formation of pigment. These granules became more marked as the chromatisation of the tissue proceeded.

On the second day:- faint blue haze developed in nuclei of the basal cells, and in more superficial cells when pigment was present in them.

Up to the fifth day the haze was deeper in colour and more distinctly granular.

Fifth day also granules showed a tendency to peripheral arrangement in the cells, and some were seen in the spaces between the prickle cells.

Tenth day granules peripherally arranged in basal cells, whose centre was clear.

The re-action remained then stationary till the fifteenth day and then gradually faded.

The reaction was proportionate to the activity of the pigment formation. He never found it present in the cutis.

He concludes then that pigment is a product of the nucleus of epithelial cells.

The nucleus is composed of two classes of substance - lypoid and proteid.

As a result of its functional activity the nucleus excretes certain substances consisting of a lypoid and a proteid portion. This is the mother substance

of pigment. He considers melanin to be contained in the proteid portion of the excretion of the nucleus. This portion on escape from the nucleus is precipitated, and remains as a foreign body in the cytoplasm of the cell. The ~~ly~~pid portion passes out of the cell and thence to the lymphatic spaces.

He explains pigment in the cutis by the assumption that it is absorbed by wandering cells from the lymphatic spaces.

He finds cutis pigment is darker in colour, more coarsely granular, less soluble in various reagents, and not so easily decolourised by hydrogen peroxide as epithelial pigment.

The cutis pigment gives no reaction with bichromide and haemotoxylin, and is therefore apparently of more stable composition and derived from that formed in the epithelium.

A pathological increase of pigmentation may be explained

1. By stimulation of epithelial cells to increased activity, by agents such as light, heat, irritants, etc.
2. By deficient drainage due to obstruction of the lymphatics of the cutis.
3. The third theory is that epithelial and cutis pigment are independently produced, by cell metabolism in the part in which they are found.

Meirowsky (Ueber den Ursprung des melanotischen

pigments der Haut u des Auges. Leipzig 1908) from experiment with Finzen light concludes that human epithelium is capable of forming pigment, and also that cutis pigment is produced by mast cells.

He also considers that connect^{ive}~~ed~~ tissue cells are capable of forming pigment.

J. Caspary (Arch. f Dermat u syph. Wien 1891 Bd. 23, S. 7 and 8) studied pigmentation in Addison's disease. He found branched pigment cells in the cutis which sent processes between the epithelial cells, and regarded the pigment-producing cells as connective tissue elements.

Ehrmann (Vrtljschr f Dermat u syph. Wien 1885 Bd. 12, S. 509) studied pigment formation in the skin of the frog. He says that in the frog's skin between the epithelium and the connective tissue there is a dense network of capillaries, surrounded everywhere by pigmented cells, which occur also to a less degree along the larger vessels. E. regarded these cells at first as active connective tissue cells which produced melanin from the haemoglobin of the blood; but later (1896 Heft. 6 Biblioth Med. Abth. Dii Derm u Syph. S 2 and 61) came to the conclusion that they were special cells derived from the meso-blast of the embryo, and designated them melanoblasts. Their function, he thought, was the production of pigment.

Karg (Arch. f anat. u entwicklungsgesch 1888 S. 391), transplanted the skin of a negro on to that of

a white, and that of a white on to a negro, and excised the portion some weeks after. He found that the transplanted black skin had become white, and the transplanted white skin had become black, and concluded that all epithelial pigment owed its origin to cells in the cutis, which carry the pigment to the epithelial. These cells he called chromatophores; he considered them to be of mesoblastic origin. He says that they transfer the pigment to the epithelial cells by means of branch^{ed} processes which penetrate the spaces between the epithelial cells, and end in the substance of these cells.

It would appear from these various researches that whereas in many cases the melanin occurs chiefly, if not wholly, in relation to the epithelial cells, and is in some way a product of their functional activity, yet nevertheless it may be

(a) Not only transferred from the epithelium to the cutis but

(b) Formed actually in relation to the connective tissue cells, either by their activity, or as a deposition in them in the nature of a foreign body.

The fact that the pigment may occur entirely in the connective tissue cells or between them and remain strikingly absent from the epithelial structures seems to exclude definitely the view that epithelial tissues are alone capable of elaborating it, and the explanation of its presence in the cutis by the assumption that it is carried to that situation

from the epithelium.

The older theory of the relation of melanin to altered haemoglobin (apart from its elaboration from the blood elements by vital cell processes) may be taken as definitely disproved.

In many cases, owing to the insufficient discrimination between true melanin, and altered blood pigment, the observations were faulty, and a further knowledge of the character and composition of melanin, has shown that it is quite distinct from the substances resulting directly from the destruction of haemoglobin such as occurred^s for instance at the site of an old haemorrhage.

Microscopical appearances in Case I.

The tissue had been hardened in formalin then treated with spirit and preserved in glycerine and water.

Sections were made at various levels of the large intestine, and at several levels from the small intestine. One portion of tissue at each level was dehydrated in alcohol, acetone, and xylol, imbedded in paraffin, and cut with the rocking microtome. Another portion was washed in water, soaked in dextrin solution and cut on the freezing microtome.

Sections were cut in each case both superficially, that is parallel as far as possible to the mucous membrane, and at right angles to it.

1. Transverse - paraffin - haemalum and eosin.

At each level of the intestine the sections showed similar appearances.

The muscular coat is perfectly normal in appearance. The nuclei stain well. There are in rare places a few pigment granules lying between the muscle cells. In many sections they do not occur in this site at all. There is in no place pigment in the muscle cells. The muscularis mucosae is healthy in appearance and contains no pigment.

The connective tissue of the mucous coat shows large masses of pigment granules. These fill a large portion of ^{the} ~~a~~ connective tissue. The ^{glandular} ~~granular~~ tubules are quite surrounded by the pigment masses, which abut closely on them, and on the muscularis mucosae. The special crowding of the pigment against the muscularis mucosae, which Pick found in most of his patients, is not evident. It appears to be evenly distributed from the surface to the muscularis mucosae. The pigment is of a rich golden brown colour, unaffected by the stain, as it appears just the same colour in unstained sections.

Besides the prevailing golden brown masses, there are here and there small particles of a deep black which correspond exactly to what Pick found in his sections, looking as he says "like adventitious impurities".

The general arrangement and shape of the pigment masses suggest strongly that they are for the most part intracellular, filling, almost completely,

rounded cells of the connective tissue. A good deal of it nevertheless is obviously extracellular, lying in scattered clumps of granules between the cells.

With higher magnification the granules of which the pigment masses are composed are better seen. In the case where these granules are collected into small masses the pigment appears shining golden brown and almost translucent. In the case where it forms larger and denser masses the appearance is duller, and much darker brown.

In the connective tissue cells - the majority of which contain pigment - many being packed with it, these rounded darker masses look almost like a nucleus in many cases, but with this stain the nuclei of the pigment containing cells is not to be demonstrated with certainty.

There is nowhere any crystalline formation of the pigment. It is universally amorphous.

Except for the presence of the pigment the connective tissue presents little pathological change.

The nuclei of the rest of the cells stain well. There is however a distinct, though slight, overgrowth of the fibrous tissue element and the vessels are in part somewhat thickened. There is no evidence of infiltration with inflammatory cells.

The epithelium on the surface is very largely gone - the small portions which remain show a catarrhal condition.

In the glands the epithelial cells are in many

cases small - they show considerable catarrh - and in many glands evidence of proliferation into the lumen of the ducts, indicating repair of desquamated cells, the condition being one of atrophic catarrh.

There is in no single instance any pigment in the epithelial cells.

2. Superficial sections show well the pigment surrounding the lumen of the ducts, approaching up to the basement membrane, but never beyond it, and the absence of pigment immediately the muscularis mucosae is reached.

3. Frozen sections Haem. and Eosin - Farrant, show the same appearances, and demonstrate clearly that the quantity of pigment in these and in the paraffin sections is the same. Therefore the treatment by alcohol and acetone has no effect whatever in dissolving the pigment.

4. With a view to demonstrating the nuclei of the cells better, a portion of tissue, after being washed in water was placed in Müller's fluid and placed in the incubator at 37° C. The Muller's fluid was changed every day, and the tissue at the end of a week was taken out and paraffin sections made of it. The sections were then stained in Carmine solution for twelve hours, and decolourised in one per cent. hydrochloric acid in rectified spirit - dehydrated and mounted in Canada balsam.

Sections treated in this manner show clearly the

nuclei of the pigment cells, sometimes obscured by pigment, sometimes clear and distinct, often pushed to one side of the cell. The stain confirms also the conclusion that a good deal of the pigment is extracellular, as no nuclear staining is seen in connection with the irregular clumps of granules lying apart from the more rounded masses occupying, and taking the shape of, the cells.

5. Frozen sections stained with Scherlach R., with Nile blue and with one per cent. osmic acid. In no case was there sign of any fatty nature of the pigment.

6. In view of Dyson's observations on melanin Professor Lorraine Smith's bichromate - haematoxylin - borax-ferrocyanide method for the demonstration of lipid substances was carried out - although Dyson states that in the case of cutis pigment he has never been able to demonstrate the formation of the blue granules which he regards as the precursors of melanin.

It was found, however, that after transference to the haematoxylin and acetic acid solution, the tissue rapidly ~~put~~^{took} on a diffuse dark blue staining, and no differentiation was discoverable.

Professor Lorraine Smith, whose advice was sought, suggested that this diffuse staining might be due to general autolysis of the tissue cells. If this were so, the haematoxylin and acetic acid solution would stain the tissues without previous bichromating. Sections were consequently treated in the way sug-

gested, but no blue staining resulted, and the cause remains unexplained.

7. Sections - superficial and transverse - frozen and paraffin, of the small intestine stained by the several methods, showed an entire absence of pigmentation. The epithelium in these sections also shows a considerable amount of separation, and this is probably large to be accounted for by post mortem change.

8. Frozen and paraffin sections were tested for the Prussian blue reaction. After treatment in the incubator in five per cent. hydrochloric acid for periods varying from one hour to twelve hours, and then with potassium ferrocyanide the reaction was in all cases negative. ✓

Micro-chemistry. Case I.

As during the chemical investigation of the tissue in mass the presence of mercury was discovered, and the other heavy metals were excluded, it became necessary to endeavour to differentiate, with the pigment in situ, between this and melanin.

This presented considerable difficulty, because the mercury would be deposited as the sulphide, which is an inert substance, incapable of solution except in reagents strong enough to destroy the substance, and melanin itself also resists the action of the usual solvents.

The sections were subjected to the action of ether, chloroform, acetone, benzol, dilute hydrochloric, sulphuric, and nitric acid (cold and warm) and dilute alkalies, and the pigment remained unchanged in all cases, both as regards colour and quantity.

Stronger solutions of the acid destroyed the sections as did also concentrated alkalies.

Chlorine water was tested on a thin film of mercuric sulphide prepared in the laboratory, and was found to decolourise it rapidly, and on treatment with a solution of sulphuretted hydrogen, the black sulphide was again formed.

This test was applied to the sections with the following result,

1. Paraffin sections exposed to the chlorine water showed in about five hours the complete decolourisation of the pigment, though none apparently was dissolved out of the tissues. On treatment with sulphuretted hydrogen solution the colour was gradually restored to the pigment, so that on comparing a section after immersion in this solution for about an hour, with an untreated similar section, the colour and quantity were almost identical.

2. Frozen sections, which were of course thicker, gave a less positive result. After immersion in the chlorine water up to a period of 24 hours the pigment though distinctly paler, was not completely decolourised. Treatment with sulphuretted hydrogen solution restored what colour had been lost.

As a control for the value of this test in differentiating mercury from melanin, dark hair was taken, washed in ether to clear it of fatty substance, and treated with chlorine water. After 24 hours the hair was bleached almost white, but no reconstitution of the colour occurred in sulphuretted hydrogen.

3. Frozen and paraffin sections were treated with a solution of iodine in water and also with a solution of iodine and potassium iodide, with a view to determining whether by their action on the mercuric salt, if such it were, the yellow iodide would be produced.

No change was however produced in the pigment, in sections treated for varying periods up to 6 hours. This would however, be explainable by the assumption that the mercury was too firmly combined for the iodine to act upon it, as would be the case with the sulphide.

4. Fresh ammonium sulphide produced no darkening of the pigment.

Chemical Investigation of the Tissue in mass - Case I.

The main objects in this investigation were as follows:-

1. The determination as to whether or not the pigmentation was due to any blood colouring matter.
2. The determination of the presence or absence of any of the heavy metals such as mercury, lead, bismuth, etc. which are known to produce pigmentation.

3. The determination as to the presence or absence of melanin.

The demonstration of melanin by chemical tests is on the whole unsatisfactory. The actual chemical composition of melanin is not understood. It seems probable that the term is used to include pigment occurring in various situations in the body, which are not all identical.

Walter Jones ("The Chemistry of the Melanins", American Journal of Physiology, Vol. II 1899, page 380) says, "The name Melanin is a generic term which is used to include all of the dark brown or black animal pigments, whether formed in the body by normal processes, or under pathological conditions. Owing in a measure to the great interest which these substances possess for the pathologist, they have been the subject of a number of researches of a chemical nature, yet for some reason these researches have been so fruitless, that at the present time we are not in a position even to define a melanin in the chemical sense; in fact we are not all agreed as to what chemical elements are necessary constituents of a melanin molecule."

It is recognised that the separation of the melanin in a pure and uncharged state from the tissue is, in view of its great insolubility, almost impossible. The only way to separate the two is to use reagents strong enough to destroy the tissue, and there is no proof that after such energetic treatment the sub-

stance obtained has not been changed considerably in composition.

The chemical reaction relied on for the identification of any pigment as melanin are shortly as follows:-

1. Insolubility in the usual solvents, such as water, ether, chloroform, etc.
2. Resistance to acids both dilute and concentrated, with the exception of concentrated nitric acid, which produces solution.
3. Resistance to dilute alkalies, but usually solution on melting with solid alkali, from which solution it can be precipitated as a yellow granular deposit (melaninic acid).
4. The production of certain bodies such as Indol, Pyrrol, and Skatol, recognised by their smell, on heating to about 300° C. with alkali. Von Fuerth (Centrbl f Allg. Pathologie Bd. 15, 1904, page 167), regards Indol as the most constant of these bodies which can be attributed to the melanin, and not to the accompanying albumen of the tissues. He found, however, that after boiling the tissue for five hours with concentrated hydrochloric acid to remove all trace of albumen there was no Indol produced.
5. The gradual bleaching of the pigment in certain reagents, especially chlorine water.
6. Quantitative analysis has yielded results so divergent that it has proved of little value. Thus Von Fuerth (Loc. cit.) in a table of various results which have been obtained, shows that the sulphur

found varied from 4.1 per cent. to nil - the carbon from 50.9 per cent. to 59.9 per cent., and so forth; evidently the pigments were originally different, or the process of extraction had changed them in varying degrees.

The tissue was treated as follows:-

1. With dilute acid, hydrochloric, sulphuric, and nitric, the tissue remained unchanged, both with cold and hot solutions.
2. Concentrated sulphuric acid produced darkening of the whole tissues but produced no solution.
3. Concentrated hydrochloric acid produced no solution of the pigment.
4. Concentrated nitric acid on heating, caused complete solution of the tissues and pigment, giving a yellow solution.

Into this solution a piece of thin sheet copper was placed. The acid was allowed to act on it for about two minutes. The copper was then removed and washed. It was dusky grey in colour, with an obvious coating over the copper. It was dried, placed in a glass tube and heated to redness. Iodine was then ^{int}roduced into the tube and volatilized. In the part of the tube removed from the copper, a well-marked yellow deposit (iodide of mercury) formed. This demonstrated the presence of mercury in fairly large amount.

5. The tissue was boiled in concentrated sulphuric acid to which from time to time concentrated nitric

acid was added, a few drops at a time. When the solution became clear after about half an hour's boiling it was evaporated to dryness. There remained a white solid residue which was easily soluble in distilled water.

Separate portions of this solution were treated by the addition of sodium hydroxide solution, solution of sulphuretted hydrogen, and solution of potassium iodide. No precipitate was formed, and thus the presence of the heavy metals was excluded. The mercury had evidently volatilized in the prolonged heating.

6. Weak alkali produced no solution in the cold or on boiling.

7. Boiling with concentrated sodium hydroxide produced disintegration of the tissue, and a liquid containing much undissolved black substance. On filtrating this a clear brown solution was obtained, and on neutralising this with hydrochloric acid a yellowish flocculent precipitate formed, which under the microscope appeared as yellow, amorphous, granular masses, resembling in appearance the melaninic acid which is described as resulting from melanotic pigment treated in the same way.

8. Heated strongly with solid alkali, there was a distinct smell of Indol and similar bodies, but unpigmented tissues treated in the same way gave much the same smell, and there can be no doubt that various organic tissues will give a like result, so that as

a test for melanin this process, though a good deal of importance is apparently attached to it, is unreliable.

9. Chlorine water produced a slight bleaching of the colour.

10. The Prussian blue reaction was negative.

Specimens of the tissue exposed for a short time in 5% hydrochloric acid, and also for 24 hours at 37° C. before treatment with potassium ferrocyanide, all gave negative results.

11. The solutions produced by boiling with strong alkali and with concentrated nitric acid were negative to the spectroscope.

12. The solution tested with nitric acid gave no bile reaction.

13. A portion of the unpigmented small intestine dissolved in hot concentrated nitric acid and tested for mercury gave a negative result, as did also unpigmented tissues from the wall of the large duct.

In view of these results the issue lay between mercury and melanin as the cause of the actual pigmentation. In many respects the reactions corresponded with those supposed to be characteristic of melanin, though in dealing with this body the process of identification consists largely in the exclusion of other substances.

An inert substance like mercuric sulphide would however share with melanin this resistance to various

reagents, and the differentiation by positive tests becomes somewhat difficult. Melanin is stated to be decolourised by chlorine water, though somewhat slowly, the reconstitution of the colour by sulphuretted hydrogen was however strong evidence in favour of the mercury, as reconstitution does not occur with melanin.

In favour of the mercury being the actual cause of the pigment were the following facts:-

1. The mercury reaction was present in the pigmented tissue.
2. It was absent in the unpigmented tissue of the large bowel.
3. It was absent in the unpigmented small intestine, and therefore was presumably not merely a contamination on the surface of the bowel.

The evidence then seems greatly in favour of this being a case corresponding to that of William's, in which the pigmentation is due to the deposit of mercury, probably in the form of the sulphide.

There is no clinical history obtainable of mercury having been taken in large quantities, though it is possible it may have been. It is scarcely conceivable that unless large quantities had been taken, such a marked change in the bowel could have been produced.

As regards the relation of this case to those described by Pick as true melanosis, one must of course accept Pick's observations. The chemical

investigation was in his cases undertaken by Prof. Boruttau, and Dr. Jacobsohn, and was apparently a very thorough one. They had in mind the possibility of pigmentation by mercury, lead, etc. and state that the presence of these metals was carefully excluded, though they do not state by what test their absence was demonstrated.

In view of these facts the resemblance of this case to Pick's is very remarkable. The macroscopic and microscopic appearances tally so exactly. The pigment in its distribution, appearance, form, relation to cells and resemblance in many of its reactions render the similarity very striking.

In discussing the question of differentiation between mercury and melanin, Pick lays stress on the fact that none of his patients suffered from any symptoms of mercurialism, such as tremor, salivation, etc. He thinks that they would certainly do so if sufficient mercury had been absorbed to produce such a deposit. In this case there was no sign of any such manifestations as far as can be judged, and therefore this point seems of little value as excluding mercury.

As to the actual mode of deposition of the pigment, two theories might be adopted.

The large gut, though its function is ill understood, is generally supposed to exercise both an absorptive power (on fluids) and an excretory one.

One may suppose (1) that the mercury has been absorbed

into the mucous membrane in a soluble form, probably as an albuminate and then deposited as a result of the action of the sulphuretted hydrogen in the bowel; or (2) that the mercury has been absorbed into the blood, and in process of excretion has reached the capillaries of the mucous membrane of the large gut; that it is taken from the blood by polymorpho-nuclear leucocytes, and meeting the sulphuretted hydrogen in the tissues becomes deposited in this way.

CASE II.

Margaret S. aged 50, died November 20th 1909.

Post mortem November 22nd 1909, by Dr. T. Shennan.

History:- Some difficulty with her speech on November 17th. On November 19th she became unconscious, and was admitted to R.I.E. in this condition. She died next day without becoming conscious.

There was a history of previous drug-taking.

Post mortem diagnosis sulphonol poisoning.

Extracts from Post mortem record:-

Heart:- no important change.

Stomach:- 25 partially dissolved tabloids were found.

By analysis these were recognised to be composed of sulphonol. The stomach was dark in colour from the outer aspect, and 8 to 10 ounces of a greenish mucous fluid were removed from it. Chronic gastric catarrh.

Intestine:- enteritis in upper part of small intestine.

No change in lower part.

Large intestine:- Brown pigmentation throughout its length.

Specimen:- hardened in formalin - treated with spirit - and preserved in glycerine and water - consists of about 14 inches of what is apparently the descending colon.

The bowel wall is thin and atrophic.

The mucous membrane shows a uniform brown pigmentation.

The colour is rather lighter than that in Cases I and III. It presents no mosaic appearance, and no areas of lighter pigmentation. It is quite uniform, and shows no lighter nor darker shade at the upper end than it does at the lower.

The lymphatics are unaffected.

CASE III.

John S. aged 66 years, died February 7th 1909.

Post Mortem February 10th 1909, by Dr. T. Shennan.

History:- Had had apoplectic seizures - obscure pain about the gall bladder. Much arterial degeneration. High blood pressure. Slight hemiplegia while in hospital a fortnight ago.

Large haemorrhage from bowel and death.

Post mortem diagnosis, cerebral haemorrhage.

Arterio-sclerotic atrophy of kidneys. Some interstitial nephritis.

Extracts from Post mortem report:-

Large and small intestines are both distended. The former is of a dark greyish brown colour. Calcareous tuberculous glands in the mesentery. Walls of jejunum are thick and oedematous.

Heart:- Both coronary arteries extensively atheromatous.

Aortic and mitral cusps thickened. Diffuse fatty change in the region of the septum.

Left Lung:- marked emphysema. Acute early broncho-pneumonia at apex of lower lobe.

Right Lung:- Emphysema. Broncho-pneumonia in rather larger patches.

Stomach:- Mucous membrane contains a few brownish spots of altered blood. The mucous membrane is atrophied.

Large intestine:- is filled with altered blood. Mucous membrane shows diffuse haemorrhage throughout, with a few superficial more recent and lighter areas of haemorrhage. There is no one special bleeding point, and bleeding has evidently come from the whole surface of the intestine.

Head:- Dura more adherent than normal. Brain on section contains a haemorrhage into the outer part of the lenticular nucleus of the left side.

Specimen hardened in formalin - treated with spirit - and preserved in glycerine and water - consists of about a foot of the descending colon. It shows an appearance almost exactly similar to Case I. It is uniformly dark brown, shows the network, or mosaic appearance well marked, and to a certain extent the arrangement of the network lines along the taenia. The areas of lighter pigmentation are not apparent. The light coloured spots, about the size of a pin's head, which Pick described, and which were not present

in Case I, are here fairly plentiful, occurring at distances at about half an inch from each other over most of the surface.

At the time of the post mortem the true condition was obscured. The bowel contained much blood, and the post mortem was made three days after death. Dr. Shennan thought that the condition at the time was due to staining of the tissue with the blood, in conjunction with post mortem change. In the process of preservation, however, all trace of deposited blood has disappeared, and he then recognised the true condition.

The pigmentation was bright brown, and typical of the appearance of true melanosis. It has none of the greenish appearance of post mortem change.

There is no sign of inflammation, nor ulceration on the mucous coat.

The other coats of the bowel are healthy in appearance. There is no sign of lymphatic involvement.

The tissue was subjected to the same investigation as in Case I.

Microscopic appearances in Case II and III.

1. Stained with haemalum.

The epithelium here also is mostly gone from the surface. Catarrh in the ducts. No pigment in any case in the epithelial cells. The pigment limited exclusively to the region between the epithelium and muscularis mucosae, with a definite increase along the

upper surface of the latter.

The pigment for the most part in rounded connective tissue cells - some extracellular. The colour of the pigment almost exactly the same as in Case I; perhaps a little darker. It is amorphous, granular, fills some cells completely, others partially. The larger and smaller granules appear, as do also the larger masses. Case III shows the pigment to be rather less in quantity than in Case II.

There is some thickening of the vessels.

The nuclei stain well. The other coats of the bowel are healthy, with good nuclear staining.

2. Superficial sections show the glands clear of the pigment, but quite surrounded by it.

3. Frozen sections show that the pigment had not dissolved in the paraffin sections, in the alcohol or acetone.

4. Carmine stain shows the nuclei of the pigment cells.

5. Scharlach R, osmic acid, and Nile blue stains for fatty substances were negative.

6. Lorraine Smith's method of bichromating produced also here a dark blue diffuse stain and no demonstration of the blue granules described by Dyson.

7. Prussian blue reaction was quite negative.

Micro-Chemistry - Cases II and III.

1. Chlorine water - applied as in Case I produced slowly a bleaching of the pigment, but on treatment with sulphuretted hydrogen the colour was not reconstituted, though there was a little darkening of the bleached pigment on prolonged treatment.

2. Ammonium sulphide produced no blackening.

3. The pigment resisted the action of the various solvents, acids, alkalies, etc. as in Case I.

Chemical Investigation of the tissue in mass - Cases II and III.

1. The behaviour with dilute and concentrated acids was identical with Case I.

2. The solution produced by concentrated nitric-acid gave, when tested for mercury, a negative result in both cases. There was no reaction for the other heavy metals.

3. With dilute alkali there was no solution.

4. With concentrated alkalies a dark solution was obtained on boiling for some time, and an amorphous, light yellow precipitate formed on addition of hydrochloric acid.

5. Heated with solid alkali there was no distinct evidence of the formation of indol or pyrrhol.

6. Chlorine water produced slowly some bleaching of the colour.

7. The Prussian blue reaction was negative.

8. Spectroscopic examination was negative.

9. In Case II the test for sulphonal was carried out. The tissue was dried in an incubator, and then heated strongly with a 1 in 2 solution of sodium hydroxide; In the presence of sulphonal, in these circumstances, a smell of garlic is obtained. The test was negative.

Cases II and III therefore are apparently true cases of melanosis.

In Case II the fact that sulphonal is known in large doses to produce haemolysis, might suggest an origin for the pigment in this process, but the strict limitation of the change to the large intestine is not characteristic of such an effect of the drug. Moreover, the pigment failed to give any Prussian blue reaction, and its appearance, both naked eye and microscopically, did not correspond to that of altered blood. On the other hand it was typical of the cases described as true melanosis.

Case III was at the post mortem actually taken for one of diffuse haemorrhagic staining. The blood tended to obscure the true condition, which only appeared later. The absence of the reaction for blood, and the typical appearances, and reactions must cause it to be regarded as analogous to the cases described by Pick.

The limitation of the pigmentation so exactly to the large intestine, must point to its being dependent on some condition present in the large and not in the small gut. The most obvious and probable factor is the putrefactive nature of the processes within the former. The ileo-caecal valve forms a sharp barrier between the small intestine, where organisms are few, and active absorption is going on, and the large, where putrefactive and other organisms are plentiful; where the bowel contents in many cases at least, stagnate, and not only is the progress of the bowel contents much slower, but actual anti-peristalsis is known to exist.

Pick concludes that the melanin is formed from the aromatic albumin compounds (Indol, skatol, etc.) which are characteristic of the large intestine, and present in larger quantities in cases where stagnation and fermentation are more marked.

He attributes this action to a ferment present in the connective tissue cells resembling tyrosinase. Whether the process is one involving the action of a ferment or not is not clear, but at least it seems evident that its deposition must be closely related to cell activity, and presumably to that of the connective tissue cells.

The essential deposition seems to be intracellular, and the extra-cellular pigment, which is in all cases in lesser quantity, is most readily explained by supposing that it results from the

destruction of pigment-containing cells.

The following is a list of Pick's Cases, and extracts from his description and conclusions:-

1. R. Virchow (Virchow's Archiv. 1847 Bd. 1, S 410 and 411).

J. Sch. died 24:8:1845 of oedema of the lungs after long treatment in hospital for fracture of the neck of the femur.

Post mortem - intestine - black colouration of the whole mucous membrane of the large intestine, from which only the glands remained free.

Microscopic examination - the pigment is present as shining granules.

2. C. J. Williams. Black deposit in the large intestine from the presence of mercury. (Trans. Path. Soc. Lond. 1867, Vol. XVIII, p. 111 to 114.)

Healthy woman 74 years. Had taken one grain of calomel every night for 43 years. Left sided pleurisy ten years before death. Later flatulence and pain in iliac regions. Pale and cachectic in last year of life. Albumin in urine for ten months before death. Death from oedema of the legs, dyspnoea, and crippling of the heart.

Post mortem - fatty degeneration of the heart. Mitral stenosis. Chronic interstitial nephritis. Atrophic cirrhosis of the liver. Gall stones. Stomach, atrophic. Jejunum and ileum, pale but fairly normal. Inner surface of the large gut black, with areas of lighter pigmentation. The

colouration began at the ileo-caecal valve, and contrasted sharply with the light colour of the small intestine. Mucous membrane smooth and shining and free from ulcers or other defects. "The whole presented the appearance of a toad's back". The origin of this colour was pigment in the sub-mucosa between epithelium and muscularis mucosae. It occurred (1) as thick opaque masses of irregular shape, (2) as small granules that lay partly separate, partly collected together.

3. G. Newton Pitt. Colon pigmented black throughout with lead (Trans. Path. Soc. Lond. 1891, Vol. XLII, p. 109).

Man, 45 years, died - granular kidneys. Had been a lead worker and had suffered from lead colic and gout. The whole small intestine appeared normal. The caecum and colon were darkly pigmented right to the anus, almost black in the neighbourhood of the caecum. In spirit the colour faded gradually.

4. H. D. Rolleston. Colon pigmented from mercury (Trans. Path. Soc. Lond. 1892, Vol. XLIII, p. 69).

Man, 64 years, died from bronchitis. Large gut uniformly pigmented. Small intestine free from pigment. Whole alimentary tract free from inflammation or ulceration.

Mic: Exam: Amorphous pigment deposited in the mucosa, apparently in and between the cells of Lieberkühns

follicles, while under the muscularis mucosae there was no trace of pigment. The patient had had syphilis at 44 years. Not known whether he had had a course of mercury then. He was treated eight months before his death for a (doubtfully) syphilitic ulcer of the tongue.

5. Grawitz (Virchow-Hirsch's Jahresberichte Der Gesmt. Med. 1892, abt. 1, S. 235 and 236).

Grawitz mentions a case similar to Pitt's. No details given.

6. Solger. Case I.

Frau K. 69 years. Ulcer of the stomach.

Post mortem cicatrices of the stomach. Senile marasmus. Oedema of the lungs. Catarrhal nephritis. Melanosis of the large intestine. Small intestine reddish grey. Large gut, mucous membrane darkly pigmented right up to the anus, the pigmentation beginning at the ileo-caecal valve. Brown back ground with numerous fine points the size of a pin's head overlying.

7. Solger. Case II.

Man 51 years. Cancer of the stomach.

Post mortem - general purulent peritonitis. Enteritis. Colitis pigmentosa.

The pigmentation of the mucous membrane begins, with a sharp margin, at the caecum; it is dark brown in colour.

8. Solger. Case III.

Man, 76 years. Senile Marasmus. Left sided pneumonia.

Post mortem - pneumonia, bronchiectasis. Catarrhal enteritis. Colitis pigmentosa. Bile stained contents in small intestine. Mucous membrane greyish red. Small haemorrhages in jejunum. No faecal content in large intestine. The mucous membrane displays irregular folding, and brown pigmentation as also in the rectum. The rectum contained thick brown scybala. The mucous membrane is smooth and shows a dark brown pigmentation with light stripes.

9. Solger. Case IV.

Man, 72 years. Cancer of the stomach.

Post mortem - Fibrous pericarditis. Hypostatic pneumonia. Oedema of the lungs. Stenosis of the colon through tumour mass. Melanosis of the large intestine.

10. Solger. Case V.

Person, 41 years.

Post mortem - Cancer of sigmoid flexure. Perforation. Melanosis of the large intestine. Mucous membrane of the duodenum and jejunum, golden brown in colour, and oedematous, especially in the jejunum.

From the caecum on begins a distinct brown pigmentation of the mucous membrane. There are

diphtheroid ulcers, of various forms and sizes, mostly transverse. These cease one metre from the ileo-caecal valve, whilst the pigment continues.

11. Solger. Case VI.

Specimen of large intestine from 1866.

Drunkard 49 years. Suffered from cir^hrosis of the liver, and died of croupous pneumonia. The preparation has through lapse of time partly lost its colour, but shows nevertheless similar appearances to the foregoing Cases.

12. Solger. Case VII.

Specimen of the large intestine from 1891.

Shows the typical melanosis of the large intestine.

13. Pick's Case I.

Caroline M. 75 years. Senile marasmus.

Constipation.

Post mortem - Chronic fibrous myocarditis. Hyperstatic pneumonia. Gall stones. Chronic cholecystitis. Senile atrophy of the kidneys. Hyperaemia of the mucous membrane of the small intestine. Melanosis of the large intestine. Mucous membrane of the rectum coloured black, the rest of the large intestine deep brown, and like a snake's skin, in contrast to that of the small intestine.

14. Pick's Case II.

W. B. 64 years.

Post mortem - Pneumonia. Chronic interstitial nephritis. Slight cir^hrosis of the liver. Atrophic catarrh of the stomach. Melanosis of the large intestine.

15. Orth-Gottingen. (Examined by Pick).

Karl J. 40 years.

Post mortem - Cancer of the pylorus with stenosis. Chronic enteritis with brown pigmentation of the large intestine.

16. Orth. (Examined by Pick).

Frau K. died 2:2:1899 from fracture of the skull. Specimen of large intestine 22 cm. long, with the lower end of the ileum. Characteristic appearance of melanosis beginning at the ileo-caecal valve.

17. Eugen Frankel. (Examined by Pick).

Man, 48 years. Died of Anthrax.

Melanosis of the large intestine.

18. Pick's Case III.

W. K. 41 years.

Post mortem - atrophic cir^hrosis of the liver. Chronic parenchymatous nephritis. Catarrhal bronchitis. Blood in oesophagus, stomach and intestine. Chronic hyperplastic gastritis. Catarrh of the small intestine. Melanosis of the large intestine.

Extracts from Pick's descriptions of his Cases.Microscopical appearances Solger's Cases I, II, III
and V.

The characteristic colouring is produced by a copious deposition of pigment in the tunica propria of the mucosa. The pigment is confined to the mucosa; only in the most superficial layers of the sub-mucosa are found here and there faint scattered traces of pigment or little groups of granules.

For the rest, the epithelium of the mucous membrane, the muscularis mucosae, and the solitary glands are free from colouring matter.

The pigment, which is grey brown, dark brown, red brown, shining rusty brown to rusty yellow or brown gold, is nowhere crystalline, and nowhere diffused through the tissues. It occurs exclusively as granules, partly in very fine granules and groups of different sizes. A certain number of larger, partly quite spherical, partly longer, partly more irregular particles of pigment are at times collected to form a conglomeration or smaller or at times larger masses.

Other more clump like elements are seen collected in heaped up masses. Other clumps are so darkly pigmented, that they look in the microscopical field like adventitious dirt particles.

The epithelium of the glands, is loosened from the tunica propria, and fills the lumen in irregular

heaps and groups.

Looking at the free surface of the mucous membrane one finds the spaces between the mouths of the glands filled with strikingly regular, delicately ramifying pigment lines.

In a section at right angles to the surface, the ducts of the glands appear as light pigment-free interruptions between the darkly pigmented tube-shaped septa.

Pick's Case I. (13).

The mucous membrane of the rectum is darkly pigmented, that of the large gut, in contrast to the small intestine, coloured deep brown, like a snake's skin.

Partly, in large speckled areas, the intensity of the colouring is a little lighter, but otherwise the appearance is quite uniform. All over, the brown surface is traversed by fine light brown lines arranged as a network, producing an exquisite mosaic appearance.

While these fine lines vary somewhat in breadth and clearness (their diameter is never more than one half a millimetre) the integrity of the netlike arrangement is nevertheless almost everywhere preserved, and only seldom a mesh is more or less broken.

The individual areas are angular, polyhedral, and of nearly the same size, and measure in their

greatest diameter up to two or three millimetres. On the slender boundary lines of the network, mostly at the points of junction, though sometimes in the middle of the line, there occur very frequently round, sharply defined, light, greyish white spots, free from pigment, and about the size of a pin's head.

A special arrangement is seen in the network in many places next the taenia coli. The meshes are arranged in the direction of the taenia. They are squares or parallelograms and so enclose rectangular areas.

The surface of the melanotic mucous membrane is quite smooth, free from ulcers, scars, or the like, that of the specimen being perhaps rather thin and showing some senile atrophy. All the other constituents of the bowel wall are healthy. The pigment is confined throughout to the mucous membrane. Outside the pigment the remainder of the gut differs in nothing from the normal.

Mic: Exam:

A surface section of the mucosa shows the stroma, round the mouths of Lieberkuhn's follicles, (which are light and free from pigment) fill^{ed} with masses of pigment, which are brown or more often golden brown, less often dark brown black.

Some of the pigment masses are very fine angular or rounded granules, some are coarser clumpy

grains, all large more or less rounded masses, large spheres, or very large regular conglomerations.

The reaction for iron is not present.

Transverse sections:- show the integrity of all the coats, serous, subserous, and muscular, the slightly atrophic muscularis mucosae, the sub-mucosa, up to the intensely pigmented mucous membrane.

This last is certainly atrophic i.e. the follicles are a little narrower and shorter than normal, but otherwise free from any change.

The epithelium is completely gone from the surface. Wherever it is retained in the follicle, it is mostly without nuclei, partly necrosed, but always free from pigment.

The stroma is in quantity and arrangement normal throughout, free from inflammatory injection and infiltration, or fibrous change, but absolutely filled with pigment. The large and largest forms, partly spherical, partly longer or more irregular, which are abundantly met with near the coarse, apparently homogeneous, and darkly pigmented, often shining, coarse masses, are seen with greater magnification to consist of small and large granules collected together.

An especial collection of pigment occurs at the upper border of the muscularis mucosae, so that the contrast between the pigmented mucous membrane and the rest of the bowel wall which is free from pigment is made more conspicuous.

In the muscularis mucosae and the rest of the bowel wall the nuclear staining is perfect.

As an infrequent exception there appears some pigment on the muscularis mucosae and in the sub-mucosa immediately underneath, either in a finely granular form in the interstices of the muscle or connective tissue cells, or inside long spindle shaped connective tissue cells in the immediate neighbourhood of small blood vessels. Especially remarkable is the freedom of the solitary follicles from pigment.

Pick's Case II.

General appearances the same. Appendix pigmented in proximal part. Pigment begins exactly at ileo-caecal valve. Mucous membrane not in this case atrophic. Rest of the bowel wall quite healthy. The same network, but there are areas of less intense pigmentation. This appearance depends not on the areas in the network, but on the fact that the boundary lines are broader and light brown in colour. The greyish white, pigment free thickenings at their places of intersection are scarcer, and the arrangement of the network along the taenia is less distinct.

Mic: Exam:

Superficial sections show the same appearances as the first case, viz. complete filling of the tunica propria between the glands with brown pigment

consisting of fine and less fine angular granules up to coarser grains, rounded masses or large clumps of elongated or irregular shape. There was no Prussian blue reaction.

The exceptional feature in this case was the presence of infrequent spindle shaped connective tissue cells, quite solitary, and filled with pigment, which were squeezed between the muscle cells of the muscularis mucosae. There was also no atrophy of the mucous membrane, and the nuclear staining was perfect.

On the surface, and in many glands the epithelium had disappeared. It was in many ducts retained, chiefly in the form of goblet cells. It is quite free from pigment. In this case can be identified true pigment cells, with a round, generally central nucleus. Carmine stained sections show these pigment cells to be of 12 to 15 micro millimetres in diameter, round or oval, or at times more angular. The appearance shows that the extra-cellular pigment had become free through the destruction of these cells.

These pigment cells are specially abundant at the boundary of the muscularis mucosae, being so closely packed that they had become polyhedral, and a dozen or more were accommodated in the space between two glands.

Orth-Gottingen's Case.

Same general appearance, network ceases at colon. Appendix more deeply pigmented ⁱⁿ ~~than~~ proximal part, more lightly in distal.

Mic: Exam:

No nuclear staining in mucous membrane; attributed to long preservation of the specimen. Mucous membrane atrophic, thin and without epithelium. There is no pigment in epithelium nor outside the mucous membrane.

Orth. Berlin.

A specimen of the ileum with appendix removed. Same network, same boundary line and light grey thickening. Pigment begins exactly at ileo-caecal valve. Arrangement of the network along the taenia not clearly marked.

Mic: Exam:

Nuclear staining in all coats perfect. Superficial epithelium gone, that in the glands retained. No sign of inflammation, scars, etc. Stroma full of pigment, almost entirely confined to pigment cells, in the form of fine golden brown granules and larger rounded drops and clumps. The pigment cells are rounded, angular, or elongated, and have a single round or elongated nucleus, more or less central, they are either filled with pigment granules or contain only a few, so that their cytoplasm is visible. There is almost no free pigment; when it

occurs it is next to destroyed pigment cells.

Pick's Case III.

Dark pigmentation of the whole gut, the caecum being the most darkly pigmented. No pigment outside the mucous membrane. None in lymphatics. No arrangement along the taenia. Whole appendix pigmented distal end more intensely.

Mic: Exam:

Superficial section as in 1314. Prussian blue reaction negative.

Transverse section:- Nuclear staining good throughout - no change in bowel wall. Surface and gland epithelium gone.

Tunica propria free from any inflammatory change, but filled with pigment cells, which are partly rounded, partly angular, partly irregular, and often arranged in groups. The pigment is amorphous, in fine or coarser granules or in rounded clumps. The cell nucleus is round, fairly well stained, central or peripheial. Through destruction of these cells some pigment has become extra-cellular, but is mostly intracellular.

There is no trace of pigment in the lymphatics or lymph glands in the mesentery.

Chemical Investigation.

Pigment was insoluble in water, alcohol, ether, acetone, chloroform, petrol, and benzol.

Insoluble in concentrated hydrochloric, nitric

and sulphuric acid, except in Case 13 in which concentrated nitric acid at normal temperature caused slight solution.

In hot alkalies the pigment was easily soluble.

One specimen yielded, when melted with solid alkali, a strong smell of pyrrol, indol, and skatol.

Iron was found in the tissue in mass but not micro-chemically.

Special tests for metals such as mercury, copper, arsenic, bismuth, lead and silver, after destruction of the organic tissue by the Fresenius-Babo method, ^{etc} ~~was~~ in all cases negative.

SUMMARY.

Melanosis of the large intestine is a definite and characteristic condition, and one of no great rarity. The pigment is true melanin with characteristic reaction.

It is limited exclusively to the large intestine, and further to the mucous membrane of the same.

It occurs chiefly as a deposition in certain definite pigment cells, these cells being generally rounded, mononuclear connective tissue cells.

It is accompanied by no other pathological change in the bowel wall. It is partly also extra-

cellular probably owing to the destruction of the pigment cells.

The pigment is always amorphous, occurring in the form of granules, never crystalized.

The epithelium is absolutely free from pigment, as are also the cells of the other coats of the bowel.

The lymphatic vessels and glands are always quite free.

The condition is found apparently exclusively after middle life, in patients suffering from various diseases, but mostly presenting some degree of debility or cachexia.

Its significance is unknown. It produces, as far as is known, no clinical symptoms by which its presence may be recognised, but it has been observed before death, in a case of prolapsus ani.

The origin and mode of deposition of the pigment are unknown but its production is apparently associated in some way with cell activity, and it is not a mere deposition of foreign substance in the tissue. It apparently depends for its production on the peculiar conditions existing in the large intestine, as opposed to those in the small. Probably the presence of putrefaction, and more or less "copro-stasis", determines in some way the change of certain bodies in the bowel to melanin.

It may be due to the production by the connective tissue cells of a ferment resembling tyrosinase,

which elaborates it from certain aromatic albuminous products (indol, skatol, etc.) (Pick Loc. Cit.).

It is closely simulated by certain metallic pigmentations, especially that produced by mercury, and to a less extent by that produced by lead, and bismuth, but may be distinguished from these by chemical tests.